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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,751	07/02/2001	Wei Wang	DX0882XK	7429

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,751	WANG ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-4, 22, and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,22 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 04 March 2003 (Paper No. 13) has been entered in full. Claims 1 and 3-4 are amended, claims 2 and 23 are cancelled, and claims 24-33 are added.

Claims 1, 3-4, 22, and 24-33 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-3 of the previous Office Action (Paper No. 12, 29 November 2002) are *withdrawn* in view of the amended specification (Paper No. 13, 04 March 2003).

2. The rejections of claims 1-4 and 22-23 under 35 U.S.C. § 112, second paragraph at pg 8 of the previous Office Action (Paper No. 12, 29 November 2002) are *withdrawn* in view of the amended and cancelled claims (Paper No. 13, 04 March 2003).

Claim Rejections - 35 USC § 112

3. Claims 1, 3-4, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of impairing movement of a CLA+ memory T cell within or to the skin of a mammal, said method comprising *locally, topically, intradermally, or transdermally administering* to said mammal an effective amount of an antibody against CTACK, whereby administration of said antibody impairs movement of a cutaneous lymphocyte-associated antigen (CLA)+ memory T cell within or to the skin of said mammal, does not reasonably provide enablement for a method of impairing movement of a CLA+ memory T cell within or to the skin of a mammal, said method administering to said mammal an effective amount of an antibody against CTACK, whereby administration of said antibody

impairs movement of a CLA+ memory T cell within or to the skin of said mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 3-6 of the previous Office Action (Paper No. 12, 29 November 2002).

The claims also recite that the movement is within the skin of the mammal and that the antibody neutralizes cutaneous-T-cell-attracting chemokine. Claim 24 recited that the administering is local, systemic, topical, subcutaneous, intradermal, or transdermal.

Applicant's arguments (Paper No. 13,04 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts the specification discloses that a CTACK antagonist is administered systemically to a mammal (pg 3, lines 7-13). Applicant argues that Pettit et al. (cited by Examiner in previous Office Action) has been misinterpreted. Applicant contends that the authors refer to the application of proteins to the skin or the taking of proteins orally as non-invasive. Applicant submits that it is a clinically accepted method to inject the patient (invasive) and deliver a solution of proteins either into the vein or (i.v.) into the subcutaneous compartment (s.c.). Applicant states that delivery by the i.v. or s.c. route will result in systemic delivery to all tissues because the s.c. fluid drains into the blood system via the lymphatic system. Applicant cites several references that demonstrate the administration of a protein antagonist (antibody) by these two routes. Applicant asserts that based on the state of the art evidenced by the cited articles, the administration of antibodies systemically is routinely used for the administration of protein antagonists and would not required undue experimentation by one of skill in the art.

Applicant's arguments have been fully considered but are not found to be persuasive. As mentioned by Applicant in the Response, systemic administration results in the delivery of the protein to all tissues. A large quantity of experimentation would be required of the skilled artisan to determine the optimal quantity and duration of systemic administration of the anti-CTACK antibody. Additionally, undue experimentation would be required of the skilled artisan to systemically administer the anti-CTACK antibody and target only a desired region of skin. Systemic administration of the antibody would be unpredictable because the skilled artisan would not be able to determine the effect the antibody would have throughout the body, especially to normal skin. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Although the specification teaches administration of a CTACK antagonist may be systemic (pg 3, line 13), this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Such trial and error experimentation is considered undue.

Although the four articles cited by Applicant (Elliot et al., Moreland et al., Pugsley et al., and Keating et al. administer a protein antagonist (i.e. antibody) to a subject, undue experimentation would still be required by the skilled artisan to systemically deliver an anti-CTACK antibody to a mammal. Specifically, the fact patterns of the four articles cited by the Applicant and the claims of the instant rejection are significantly different. For instance, the articles disclose treating rheumatoid arthritis and Crohn's disease with protein antagonists, such as antibodies. Briefly, rheumatoid arthritis is a chronic, systemic inflammatory disease that is characterized by synovial inflammation and structural damage of articular cartilage and

subchondral bone (Bondeson et al. Int J Clin Pract 55(3): 211-216, 2001; pg 211, col 1). Crohn's disease is a chronic granulomatous inflammatory disease that may affect parts of or the entire gastrointestinal tract (Bondeson et al., pg 214, col 1). However, the claims of the instant application are directed to impairing the movement of a CLA+ memory T-cell within or to the skin of a mammal. Systemic administration of a protein antagonist in *internal* inflammatory disorders such as rheumatoid arthritis and Crohn's disease would not necessarily be predictive of the systemic administration of an anti-CTACK antibody to impair movement of a CLA+ memory T-cell within or to the *skin*. As mentioned above, it is not clear how one skilled in the art would be able to target the desired area of skin with a systemically administered antibody without affecting all skin.

Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily impair movement of a CLA+ memory T-cell within or to the skin of a mammal by systemic administration of an anti-CTACK antibody.

Furthermore, the Examiner acknowledges that it is a clinically accepted method to inject the patient with a solution of proteins. However, Pettit et al. was cited by the Examiner to indicate the state of the art at the time the invention was made. At pg 345, col 2 of Pettit et al., it

is stated that new developments in systemic administration involve prolonging the action of the circulating proteins. Also, proteins and peptides administered systemically still must resist clearance via molecule filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Therefore, the state of the art establishes the unpredictability of systemically delivering proteins to a mammal.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to systemically administer an anti-CTACK antibody to a mammal and to impair movement of a CLA+ memory T-cell within or to the skin, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the state of the art which establishes the unpredictability of delivering proteins systemically to a subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4. Claims 22 and 26-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a patient suffering from contact allergen-induced skin inflammation comprising locally, topically, intradermally, or transdermally administering an effective amount of an antibody against cutaneous-T-cell attracting chemokine (CTACK), does not reasonably provide enablement for a method of treating a patient suffering from a skin disorder comprising administering an effective amount of an antibody against cutaneous-T-cell-attracting chemokine (CTACK). Furthermore, the specification is enabling for a method of treating a patient suffering from allergic-contact dermatitis comprising locally,

topically, intradermally, or transdermally administering an effective amount of an antibody against cutaneous-T-cell attracting chemokine (CTACK). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for originally filed claims 22-23 at pg 6-8 of the previous Office Action (Paper No. 12, 29 November 2002).

The claims also recite that the skin disorder is inflammation, allergic-contact dermatitis, psoriasis, wound healing, cancer, carcinoma, infection.

Applicant's arguments (Paper No. 13, 04 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification discloses treating a patient suffering from a skin disorder by administering an antagonist against CTACK (pg 5, 10). Applicant also argues that the specification provides guidance as to what skin disorders should be treated by CTACK. Applicant explains that CTACK production is up-regulated by the pro-inflammatory cytokines TNF-α/IL-1β in vitro and downregulated by glucocorticosteroids in vivo. Applicant states that TNF-α plays a role in the pathogenesis of inflammatory and autoimmune diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification of the instant application teaches that BALB/c mice are treated with 0.5% di-nitrofluorobenzene (DNFB) on the shaved abdomen. One day five and six, the mice receive intraperitoneal injections of neutralizing antibodies against mCTACK. Two hours after the injection, mice are challenged with 0.2% DNFB on the left ear and ear swelling is

monitored (pg 78, lines 23-30). Histological analyses indicate a reduced skin thickness in anti-mCTACK-treated mice and monitoring of challenge-induced ear swelling confirms a significant suppression of skin inflammation in anti-mCTACK-treated mice when compared to mice injected with isotype control (pg 80, lines 13-18). Furthermore, the specification teaches that draining lymph node and spleen cells of sensitized BALB/c mice are labeled with CFSE and transferred into naive mice, pretreated with neutralizing anti-mCTACK or isotype before contact allergen challenge (pg 80, lines 26-30). Challenge-induced ear swelling is also monitored and a significant suppression of skin inflammation is confirmed (60-85% in 5 different experiments) in anti-mCTACK treated mice compared to control (pg 80, lines 19-20). Extraction and quantification of skin-infiltrating CFSE+ lymphocytes from allergen challenged mouse ears show anti-mCTACK treated mice have about 37% less CFSE+ skin-infiltrating lymphocytes compared to isotype control (pg 81, lines 2-3). The specification also discloses that analyses using a total lymphocyte gate indicate that anti-mCTACK treated mice who receive adoptively transferred cells show about 31% lymphocytes present in the skin compared to isotype-treated control mice (pg 81, lines 4-6).

The specification of the instant application does not teach treating a patient suffering from all possible skin disorders with anti-CTACK antibodies. Although the specification may provide guidance as to what skin disorders should be treated by CTACK or anti-CTACK antibodies (pg 10-11), this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. Furthermore, although Applicant indicates that CTACK is upregulated by TNF-α/IL-1β in vitro and TNF-α plays a role in the pathogenesis of inflammatory and autoimmune diseases, including rheumatoid arthritis,

Crohn's disease, and psoriasis, the specification does not disclose that CTACK is specifically involved in these diseases and others (such as carcinoma and wound healing). Undue experimentation would be required of the skilled artisan to identify individuals with such a disease and determine the role or expression of CTACK in the pathogenesis of these diseases. Such information is necessary, especially in the determination of the optimal quantity, duration, and type of administration of anti-CTACK antibodies. Additionally, the various diseases and disorders disclosed in the specification at pg 10-11 and mentioned above, have different pathophysiologies. For example, psoriasis is characterized by hyperplastic epidermal keratinocytes and infiltrating mononuclear cells (pg 10, lines 12-14). Rheumatoid arthritis is a chronic, systemic inflammatory disease that is characterized by synovial inflammation and structural damage of articular cartilage and subchondral bone (Bondeson et al. Int J Clin Pract 55(3): 211-216, 2001; pg 211, col 1). A carcinoma is a malignant neoplasm derived from epithelial cells, which displays uncontrolled cellular proliferation and a tendency to invade adjacent tissues and to spread to distant sites by metastasis. One skilled in the art would not be able to predict from the allergen contact experiments of the instant specification that anti-CTACK antibodies would be able to treat all possible skin disorders, such as cancer or psoriasis, which have different pathophysiologies.

It is also noted that Homey et al. (Nature Medicine 8: 157-165, 2002) does indicate that CTACK and its receptor, CCR10, are expressed more strongly in acute or chronic skin lesions of atopic dermatitis or psoriasis patients compared to nonlesional patients and healthy controls (pg 157, col 2; pg 158). However, the experiments in Homey et al. support the instant specification in that neutralization of CTACK-CCR10 interactions, impairs *allergen*-induced lymphocyte

recruitment to the skin and suppresses *allergen*-specific skin inflammation (pg 160, col 2; pg 161).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to treat all possible skin disorders with anti-CTACK antibodies, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of treatment of all possible skin disorders, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
May 17, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER